REMARKS

Claims 1-38 are pending in this application. All the pending claims have been rejected for obviousness under 35 U.S.C. § 103(a).

Applicants respectfully request that the Examiner reconsider the patentability of the inventions of the claims.

The Section 103(a) Rejection

Claims 1-38 were rejected under 35 U.S.C. §103(a) for obviousness over Hinchliffe et al. in view of Hoffman et al., Buxton, and Henry et al. Applicants respectfully disagree with the factual and legal bases for the obviousness rejection. None of these references individually or collectively teach or suggest the claimed yeast cells of the present invention.

Applicants respectfully submit that the teachings of Hinchliffe et al. are irrelevant to the present invention. Column 3, lines 59-65 of Hinchliffe et al. cited by the Examiner is irrelevant for several reasons. First, the present invention is not directed to "a genetically modified yeast which is capable of expressing a heterologous gene to produce high levels of a commercially important peptide." (Emphasis added). Applicants' genetically modified yeasts are used to produce inositol and insitol-containing phospholipids. The INO1 gene is not being claimed, but is employed as the "gene of interest" for the production of inositol and inositol-containing phospholipids.

Hinchliffe et al. at Col. 3, lines 63-65 teach that "2 μm based vectors . . . frequently constitute the vector of choice . . . ." Hinchliffe et al. also teach that in brewing yeast (Col. 4, lines 22-35) "the recombinant genes present in yeast should, so far as possible, be restricted to the 'gene of interest' and adjacent yeast regulatory genes . . . . [I]t is desirable that the genetically modified yeast should not possess extraneous DNA sequences such as those which are derived from the bacterial portion of the recombinant plasmid." Hinchliffe et al. continue at Col. 5, lines 25-45 to teach the virtues of "the 2μm based disintegration vector of the present invention" in the absence of extraneous bacterial plasmid DNA sequences.

The problem with the foregoing teachings is that the 2μm based disintegration vectors of Hinchliffe et al. can never be used to provide integrated functional copies of the INO1 gene, of any other gene of interest for that matter, which are inserted into target gene mutation loci of a host yeast. 2μm plasmids are extrachromosomal and can never be used to integrate into the host yeast's chromosome. In brief, Hinchliffe et al. only discusses high copy number 2μm plasmids.

The further discussion of Hinchliffe et al.'s teachings of a yeast plasmid with selection gene markers such as LEU2, etc., a 2μm origin of replication, and a gene of interest which upon transformation into yeast undergoes FLP-mediated recombination to delete any bacterial DNA does not "anticipate" the instant claims. Applicant's claims are all directed to yeast cells and their genomes, not plasmids. Applicants' claims

do not recite any plasmids, let alone integration plasmids with yeast origins of replication. Applicants note in passing that FLP-mediation is not a 100% efficient process and some yeast strains transformed with such 2μm disintegration plasmids may contain a mixture of plasmids, with some containing bacterial drug resistance marker sequences and others without, which is also shown in Figure 9 and at Col. 9, lines 41-47.

Merely for the purpose of clarification applicants' definition of the term "yeast integration plasmid" at p. 13 lines 9-12, p. 29, lines 4-19, pp. 29-30, bridging lines 31-5, and page 29, lines 4-19 of the specification requires that any yeast origin of DNA replication must be removed from the yeast integration plasmids after a necessary amplification step in a yeast host so that the plasmids cannot autonomously replicate in the host yeast strain that is to be genetically modified. However, as stated above, none of the pending claims recite plasmids, as contrasted with the parent application, now U.S. Patent No. 6,645,767.

The relevance of applicants' integration plasmid definition is that nowhere in Hinchliffe et al. is it ever taught or suggested that the 2μm sequence must be deleted from the plasmid to allow the plasmid to integrate into a host's genome or that it is at all desirable even to integrate. Hence, the teachings of Hinchliffe et al. only relate to 2μm-derived vectors which autonomously replicate in yeast. After the FLP-mediated recombination has taken place, the Hinchliffe et al.

plasmids still contain the 2μm origin of replication which means that those plasmids do not integrate into the host genome ever.

Further, because the Hinchliffe et al. 2μm plasmids do not integrate into the host genome and only exist episomally, they do not contain any gene (i.e., LEU2, URA3, TRP1) that can function as a targeting gene marker to insert the gene of interest into the yeast genome. By contrast, applicants' claims require genes of interest to be inserted into target gene mutation loci in the host yeast's genome.

Hoffman et al.'s teaching of co-expression in diploid yeast of two genes of interest from separate plasmids bearing 2μm origins of replication adds nothing to the teachings of Hinchliffe et al. that would render the claimed inventions obvious. Again, the use of 2μm plasmids by Hoffman et al. means that there is no possible way that genes of interest will be inserted and integrated into a host yeast's genome. Hoffman et al.'s use of multiple gene markers such as LEU2d and TRP1/URA3 has no relationship to the use of these or similar gene markers by the applicants, bearing in mind a method is not being claimed. Hinchliffe et al's gene markers are only used for selection and maintenance of the episomal plasmids in yeast and can never be used for targeting because Hinchliffe et al's plasmids are 2μm-based and therefore never integrate into a host yeast genome. In sum, these are simply gene markers on 2μm plasmids that are independent of cell or chromosomal division.

Hoffman et al. also teaches nothing about inserting multiple copies of a gene in a haploid yeast as recited in the claims.

The Examiner further states:

> While neither of the two markers on a plasmid is used for targeting (integration), this limitation in Applicants' claims is merely a recitation of intended use, and the structure of the markers on Hoffman et al.'s plasmids could function in this way, and thus the recitation of intended use for either marker does not confer patentability . . . . .

(Emphasis added.)

Applicants respectfully submit that they are not claiming any plasmids, only yeast cells. Thus the quoted language does not appear to be relevant to claims directed to yeast cells. Applicants do however believe it is relevant to say again that Hoffman et al.'s markers are only used for selection and maintenance in yeast and can never be used for targeting because Hoffman's et al.'s 2μm-based plasmids never integrate into a host yeast's genome. So long as the plasmids maintain a 2μm sequence, this will always be the case. The remainder of the Examiner's remarks about Hoffman et al.'s teachings in light of them not using integrative plasmids regarding various S. cerevisiae haploid strains, auxotrophies, mating types, and mating strains to form a diploid containing two plasmids which express two different genes are irrelevant. Hoffman et al. provides no teachings regarding any way to

integrate copies of a gene of interest into a yeast cell. That Hoffman et al. do not teach plasmids without drug resistance genes is simply an additional point of irrelevance.

The Buxton reference similarly adds nothing to the teachings of Hinchliffe et al. and Hoffman et al. to render the claimed invention obvious

The Buxton's teachings of the desirability of expressing foreign genes in yeast with vectors that avoid the use of bacterial DNA, and its teachings of making plasmids to that end are nonetheless irrelevant because Buxton only teaches plasmids that contain the 2μm sequences, meaning the plasmids are episomal and not integrative. Buxton neither teaches nor suggests anything about how to make yeast integration plasmids that do not contain bacterial DNA.

As to Buxton's teachings about avoiding bacterial DNA, the first method of which the Examiner says is similar to that of Hinchliffe, et al., such teachings are similarly lacking in relevance in light of the requirement in applicant's claims that genes of interest be integrated into the host's genome. The plasmids contain bacterial fragments until the yeast recombination occurs, but more importantly, such plasmids do not integrate due to the presence of the 2μm element. The second way Buxton prepares plasmids, described at Col. 5, lines 50-60, uses a eukaryotic host, preferably yeast, to carry out the plasmid DNA recombination to excise the bacterial DNA. However the resulting plasmid still contains the 2μm sequence and is therefore not one that can integrate either. The use of yeast

genes such as URA3 and LEU2 are only used by Buxton as traditional yeast selection yeast markers and remain extrachromosomal, nonintegrated, as discussed above for Hoffman, et al.

The Examiner has further said: "While Buxton's plasmids are not integration plasmids in the usual sense of the word, because they have yeast origins of replication, Applicant's claims, as currently worded, also encompass plasmids with yeast origins of replication." Applicants respectfully disagree with this statement because there is no unusual sense of the word "integration" involved. Plasmids either integrate into a host yeast genome or they do not. Further, applicants are not claiming any plasmids, only yeast cells. The plain fact is that Buxton's plasmids are not plasmids capable of integrating into yeast. The present application clearly teaches that if the plasmid amplification step is carried out in yeast, any yeast origin of DNA replication must be excised so that the resulting plasmid is always one that integrates into the locus of a yeast genome. There is no teaching or suggestion in Buxton that a yeast origin of replication must be excised to allow for integration of genes of interest into a host yeast genome.

Applicants respectfully submit that the addition of the teachings of the Henry et al. reference to the teachings of the three above-discussed references does not render the claimed inventions obvious. The plasmids of Henry et al. contain a bacterial drug resistance gene which are integrated into the host yeast genome. The plasmids taught by Henry et al., also

are targeted only to one locus, the URA3 locus, and there is only a URA3 marker in the Henry et al. plasmid. There is no teaching in Henry et al. that other target gene mutation loci can be used to stably integrate multiple copies of genes into a host genome. There is no teaching in Henry et al. as to the desirability of eliminating bacterial drug resistance genes in the construction of its yeast cells and certainly no teaching of how to achieve that goal.

With respect to the incorrect legal basis of the present rejection, the Federal Circuit has made quite clear that arbitrary combinations of references do not render claimed inventions obvious absent a suggestion in the references, taken as a whole, that would suggest the desirability of the combination. In other words, the focus is on whether it would have been obvious to make the combination. In re Sernaker, 702 F.2d 989, 995-96, 217 U.S.P.Q. 1, 6 (Fed. Cir. 1983); Union Carbide Corp. v. American Can Co., 724 F.2d 1567, 1575, 220 U.S.P.Q. 584, 591 (Fed. Cir. 1984); Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co., 730 F.2d 1452, 1462, 221 U.S.P.Q. 481, 488 (Fed. Cir. 1984). The Examiner has not pointed to any specific evidence in any of the references which suggests the desirability of combining the references which would lead one of ordinary skill in the art to the claimed yeast cells. Without a suggestion to combine the references, the only conclusion supported by the record is that the rejection was made impermissibly using hindsight.

As to the Examiner's conclusion of obviousness, it seems to be an assertion of the judicially disapproved "obvious to try" standard. In re O'Farrell, 853 F.2d 894, 7 U.S.P.Q.2d 1673, 1681 (Fed. Cir. 1988).

The Federal Circuit has further admonished that the claims cannot be used as a frame, and the naked parts of separate prior art references then be employed as a mosaic to recreate a facsimile of the claimed invention. W.L. Gore & Assocs., Inc. v. Garlock, Inc., 721 F.2d 1540, 1552, 220 U.S.P.Q. 303, 312 (Fed. Cir. 1983).

Even accepting the legally incorrect premise of the rejection, it is clear that a case of prima facie obviousness has not been made out. Contrary to the Examiner's assertion, the combined teachings of the prior art provide no motivation whatsoever to arrive at the claimed invention of yeast cells. A reference also must be considered as a whole, and portions arguing against or teaching away from the claimed invention must be considered. Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc., 796 F.2d 443, 448-49, 230 U.S.P.Q. 416, 420 (Fed. Cir. 1986).

Applicants have shown above that the cited references Hinchliffe et al., Hoffman, et al., and Buxton do not teach yeast integration plasmids at all because they all contain the 2μm element, thus no gene of interest can be inserted into target gene mutation loci of a host yeast cell as required by the claims. While Henry et al., does teach a yeast integration

plasmid, that plasmid contains a bacterial drug resistance gene and is further targeted to only one loci in a host yeast genome.

Contrary to the Examiner's assertions there is no motivation to combine the teachings of the references at all, and even if there were, there is nothing that would make yeast cells of the present invention obvious. Applicants have shown above that there simply is no suggestion in the cited references that would allow one skilled in the art to combine the cited references with such widely divergent teachings.

Specifically applicants submit that the teachings of the Henry et al. reference as to its integration plasmid are not combinable with those of the other references which only relate to plasmids containing the 2-micron element since while only Henry et al. teaches integration nothing is taught about avoiding bacterial DNA sequences. Additionally, Buxton, at Col. 1, lines 21-34 teaches away from the present invention because Buxton points out the disadvantages of integration plasmids, such as low transformation rates and low copy number, and that is the only way the integrated gene copies can be achieved in applicants' inventions. Additionally Hinchliffe et al. at Column 3 lines 59-65 teach that 2-micron based vectors have proven to be the vector of choice to provide high copy numbers of genes of interest, not integration plasmids. There is simply no motivation in the cited art to construct yeast cells containing one or more copies of a gene of interest stably integrated at specific loci in a yeast host that may not contain bacterial resistance genes.

With respect to the Examiner's comments on the second full paragraph of page 5 of the Office Action, applicants respectfully disagree regarding purported motivation. As discussed above, Hinchliffe et al., Hoffman et al. and Buxton were not expressing sugars and phospholipids and the means they were using to achieve expression of peptides all involved plasmids with the 2-micron element which precludes insertion and integration of a gene of interest into a host yeast which is required in applicants' claimed cells. The discussion of use of marker genes such as LEU2 and complementation of auxotrophies are not relevant to the present claims as discussed above since there must be integration into a host yeast genome. Applicants also note that its yeast cells do not always have to be prototrophic, and complementing auxotrophies does not always have to be carried out to obtain the claimed product cells. As to lack of motivation to avoid drug resistance genes at the bottom of page 5 of the Office Action, as discussed above, the plasmids taught by Hinchliffe et al. contain drug resistance genes until the FLP recombination has occurred in a yeast host. As also pointed out above, this process is not efficient and cannot be counted on to yield yeast hosts that contain stably integrated plasmids that do not contain any bacterial drug resistance genes. Further, Buxton's second ("direct") method still yields a plasmid with the 2μm element that cannot integrate into a yeast host.

As to motivation regarding Hoffman, et al. at the bottom of page 5 to mid-page 6 of the Office Action, the two 2μm

plasmids in that reference containing alpha globin and beta globin genes are not disintegrative and will never undergo FLP-mediated recombination to excise the bacterial DNA sequences. Thus they cannot possibly integrate into a host yeast genome. There is no motivation provided by this reference to arrive at the claimed invention.

Applicants further disagree that there would have been motivation to construct a suite of plasmids without bacterial DNA. Since Hinchliffe et al., Buxton, and Hoffman et al. teach plasmids that cannot integrate into a host genome, it simply makes no sense to even ponder how a suite of plasmids could be arrived at by one of ordinary skill in the art. Markers, different genes, and complementation of auxotrophies simply cannot have lead one of ordinary skill in the art to the claimed cells since Hinchliffe et al. Hoffman et al. and Buxton do not teach methods that lead to integration of genes of interest. A plasmid based on Hoffman et al. containing 2μm, URA3, LEU2, and TRP1 and not containing any bacterial DNA as suggested by the Examiner would still not be useful at all to arrive at the claimed invention.

The proposed combination of the teachings of Henry et al. with those of Hinchliffe et al, and Buxton discussed in the last paragraph of page 6 of the Office Action is not possible. The Henry et al. teachings cannot be combined with the 2μm teachings of the other three references as to 1) how to integrate one/multiple copies of INO1 into the URA3 locus without inherently integrating a drug resistance gene; and 2)

how add copies of the gene of interest into any target gene loci other than URA3 which would increase the stability of the yeast cell.

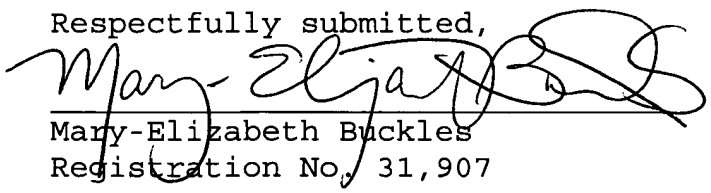
Applicants respectfully submit that none of the references, considered individually or in proper combination, teach, suggest, or disclose the claimed yeast cells as claimed. Accordingly, applicant requests the Examiner to consider and withdraw the rejection of Claims 1-38 under 35 U.S.C. § 103 over Hinchliffe et al. in view of Hoffman et al., Buxton, and Henry et al.

CONCLUSION

In view of the above remarks, it is submitted that the claims are in condition for allowance, and reconsideration of the rejection is requested. Allowance of Claims 1-38 at an early date is respectfully solicited.

If the Examiner notes any further matters which she believes would be expedited by a telephonic interview, she is requested to contact Mary-Elizabeth Buckles at the telephone number listed below.

Respectfully submitted,



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Filed: August 23, 2005